Method and apparatus for making a tablet product

Field of invention

This invention relates to a method and apparatus for forming a tablet product. This invention has particular application to loading a container (e.g. a blister of a blister pack) with a defined quantity of a medicament product in tablet form.

Background to the invention

The use of blister packs to contain medicaments in tablet form is well known. The blister packs usually consist of a base sheet in which blisters are formed. The blisters are arranged on the base sheet for loading with tablet form medicament product. A lid sheet is applied to cover the filled blisters and the two sheets are sealed together to form a blister pack.

There can, however, be problems associated with methods of filling the blisters with medicament product. Medicament product can tend to be attracted to the base sheet surface rather than to the blister pockets. This can result in ineffective loading of the blisters, create mess and potentially cause problems with adherence of the lid sheet to the base sheet.

In earlier PCT Patent Application No. WO 00/71419, the Applicant described that the potential problem of powder adherence in filling blister packs can be overcome by using a filling method utilising a perforated plate to mask the base sheet surface during filling to avoid covering this area with powder and a director (e.g. a director blade) to direct the powder into the perforations of the plate. The perforated plate is moved into contact with the appropriate areas of the blister strip during filling and then moved away at the end of the method and can be reused in each cycle. This filling method can also be used to fill other types of containers e.g. injection moulded

plastic pockets, capsules or bulk containers. Developments of the method can also be used in the production of containers loaded with medicament tablets.

The Applicant has now found that the above loading method may be improved when the perforated plate and director blade are moved in a rotary fashion relative to each other. When such a rotary relationship exists between these two components, faster methods of tablet production are enabled including those operable on a continuous rotary basis.

Summary of the invention

According to one aspect of the present invention there is provided a method of forming a tablet product which comprises:

a) closing off a perforation in a perforated plate;
b) directing powder into said closed-off perforation by the sweeping action of a first director blade spaced from said perforated plate;
c) compacting said powder in the closed-off perforation to form a tablet; and
d) transferring said tablet from the closed-off perforation,

characterized by relative rotary motion of the perforated plate and said first director blade.

Suitably, the tablet is transferred to a container (e.g. a bulk tablet container or a blister pack).

The present invention requires relative rotary motion of the perforated plate and the first director blade. That is to say, the perforated plate and first director blade move relative to each other and the motion is in a rotary sense.

It is not necessary that either the plate or the director blade be configured to rotate about the other. More typically, one component rotates about an axis and the other component is either (a) held static at a defined radial point separate from that axis; or (b) rotates about a

second axis. In any case, it may be appreciated that the overall relative rotary motion will define a relative path (i.e. direction) of motion.

In one aspect, the first director blade is held static and the perforated plate moves in rotary fashion relative thereto.

In an alternative aspect, the perforated plate is held static and the first director blade moves in rotary fashion relative thereto.

In a further aspect, both of the first director blade and the perforated plate move in rotary fashion. In other words, both are rotated such as to also result in relative movement therebetween. Embodiments are envisaged in which the first (and any other) director blade rotates at a different speed from that of the rotating perforated plate, but about a common rotational axis. Other embodiments are envisaged in which the axes of rotation are different (e.g. perpendicular).

In one aspect, the perforated plate is in the form of a planar disk, particularly one that is mountable for rotation about an axis. Suitably, the disk comprises plural perforations set out in circular fashion at a defined radial separation from the rotational axis. In one aspect, the disk comprises plural sets of perforations arranged in circular fashion concentric to each other at defined radial separations from the rotational axis.

The method requires closing off a perforation in a perforated plate. That is to say, it requires closing off an open end of a perforation to form a well into which powder may then be directed.

In one aspect, the closing off is achievable by the use of a blanking plate.

In another aspect, the closing off is achievable by the use of a blanking pin inserted into the perforation. Preferably the blanking pin is moveable within the perforation to adjust the volume of the closed-off perforation.

In a further aspect, the closing off is achievable by placing a container in registration with the perforation.

Suitably, the diameter of the closed-off perforation is between 1.5 and 15mm. The perforation may be a variety of shapes, such as square, circular, oval or rectangular.

The powder is directable by the action of the first director blade moving relative to the perforated plate. This relative movement creates a sweeping action, which acts such as to direct powder into a closed-off perforation.

Preferably, the first director blade (and any other director blade) presents a forward acute angle to the path of relative motion. The path of motion is defined by the relative rotary motion of the perforated plate and the first director blade. In this case, the angle between the direction of the (sweeping) path and the first (and any other) director blade is less than 90° (i.e. acute). Preferably the forward acute angle is between 1 and 60°. More preferably the forward acute angle is between 5 and 25°.

In a further aspect, the first (and any subsequent) director blade presents multiple forward acute angles to the path of relative motion. Such a first (or any subsequent) director blade is typically articulated or curved.

It is also possible, but less preferred to use a first (and any subsequent) director blade presenting a perpendicular or forward obtuse angle to the path of relative motion.

Optionally, the first director blade has plural movements relative to the perforated plate. The number of plural movements can be varied according to the flow properties of the powder to help ensure that the powder has a uniform density, resulting in more accurate dosing. Passing a director blade across the perforated plate more than once may in some circumstances be more economical than having multiple blades, although the time taken to fill the closed-off perforations may be greater than when using multiple blades.

Suitably, a thin layer of powder is left on the perforated plate after movement of the first director blade. Preferably the depth of said thin layer of powder is from 3 to 20 mm. More preferably the depth of said thin layer of powder is from 4 to 8 mm.

Suitably, the powder is directable by at least one subsequent director blade. Said at least one subsequent director blade and the perforated plate move in rotary fashion relative to each other. Preferably, the at least one subsequent director blade moves along the perforated plate at a lower level than that of the first director blade. This ensures that the at least one subsequent director blade can move through the thin layer of powder left by the first director blade and not just along the surface of the powder.

Suitably, the distance between the level of movement of the first director blade and the at least one subsequent director blade is 0 to 12 mm. More preferably, the distance between the level of movement of the first director blade and the at least one subsequent director blade is 1 to 3 mm. A second subsequent director blade would move along the perforated plate at a lower level to that of a first subsequent director blade.

An additional aspect of the present invention comprises removing excess powder from said perforated plate subsequent to directing powder into the perforation. Preferably the excess powder is removed by the action of a wiper. It will be appreciated that typically said wiper and the perforated plate are moving in a relative rotary sense. The wiper is typically a blade composed of stainless steel and moves in close proximity to the surface of the perforated plate to ensure that excess powder is not transferred to the blind cavity.

Suitably, the contents of the perforation are transferable by the action of a transfer pin. The pin is inserted into the perforation, transferring the tablet formed from the compacted powder through to a container.

In one aspect, transfer of the contents of the perforation to the container comprises:

a) reopening the perforation;
b) placing the container in registration with the perforation; and
c) transferring the contents (tablet) of the perforation into the container.

In another aspect, the contents (tablet) of the perforation are transferable by the action of a vacuum system. Preferably the vacuum comprises a vacuum head and at least one vacuum cup.

An additional aspect of the present invention comprises compacting the powder in the perforation.

Suitably, the powder is compacted to a tablet volume of between 20 and 50%, for example 30 to 45%, of the original volume of powder in the closed-off perforation.

In one aspect, the powder is compacted to form a dense tablet.

Suitably, the powder is compactable by the action of a compacting pin. Suitably, the transfer pin and the compacting pin are integral. More preferably the transfer pin and the compacting pin are identical.

Suitably, the container is a blind cavity. Preferably, the blind cavity is selected from the group consisting of a blister pocket, an injection moulded plastic pocket, a capsule and a bulk container. A blister pocket or injection moulded plastic pocket may form part of an elongate strip used in inhalation devices.

An additional aspect of the present invention comprises applying a lid to the container to protect the contents therein. The lid may then be sealed to the container.

In a particular aspect there is provided, a method of loading each of plural blisters arranged in series on an elongate blister strip with a tablet product which comprises:

a) closing off plural perforations in a perforated plate, said plural perforations being arranged in series;
b) directing powder into said plural closed-off perforations by the sweeping action of a first director blade spaced from said perforated plate;
c) compacting said powder in each of the plural closed-off perforations to form a tablet; and

d) transferring said tablet in each of the perforations to a corresponding blister of said elongate blister strip,

characterized by relative rotary motion of the perforated plate and said first director blade.

Suitably, in the transferring step, each perforation of the perforated plate is serially brought into registration with the corresponding blister of the blister strip. Preferably, at the point of registration the perforated plate is rotating and the blister strip is moving on a linear path.

Suitably, the perforated plate is in the form of a planar disk, particularly one that is mountable for rotation about an axis. Suitably, the disk comprises plural perforations set out in circular fashion at a defined radial separation from the rotational axis. In one aspect, the disk comprises plural sets of perforations arranged in circular fashion concentric to each other at defined radial separations from the rotational axis.

In one aspect, each blister of the elongate strip is serially brought into registration with a corresponding perforation on the disk by relative movement of the blister strip in relation to the circular series of perforations on the disk. Embodiments are envisaged in which the disk moves and the strip is kept still or in which the disk is kept still and the strip moves or preferably, in which both the disk and the strip are moving (e.g. disk rotating and strip moving in linear fashion to bring about the desired registration).

Suitably, the powder, and hence the formed tablet comprises a medicament. Optionally, other inert pharmaceutically acceptable such as lactose or another sugar may be present together with the medicament.

According to another aspect of the present invention there is provided an apparatus for loading a container with a defined quantity of product, which comprises:

a) a perforated plate;
b) a closure for reversibly closing off a perforation in the perforated plate;

c) a director for directing powder into said closed-off perforation, said director comprising a first director blade spaced from the perforated plate;
d) a compactor for compacting said powder in the closed-off perforation to form a tablet; and
e) a transferor for transferring said tablet from the closed-off perforation.

wherein the perforated plate and said first director blade are movable in a relative rotary fashion.

In one aspect, the first director blade is held static and the perforated plate is movable in rotary fashion relative thereto.

In another aspect, the perforated plate is held static and the first director blade is movable in rotary fashion relative thereto.

In a further aspect, both of the first director blade and the perforated plate are movable in rotary fashion. Different co-rotatory embodiments are envisaged, as described hereinbefore.

The perforated plate forms the basis for a powder reservoir and may have sidewalls to form a (walled) container suitable for holding powder.

In one aspect, the closure comprises a blanking plate.

In another aspect, the closure comprises a blanking pin inserted into the perforation. Suitably the blanking pin is moveable within the perforation to adjust the volume of the perforation.

In a further aspect, the closure comprises the container placed in registration with the perforation.

Suitably, the diameter of the closed-off perforation is between 1.5 and 15mm. The perforation may be a variety of shapes, such as square, circular, oval or rectangular.

Suitably, the first (and any subsequent) director blade presents a forward acute angle to the path of relative motion. Preferably, the forward acute angle is between 1 and 60° such as between 5 and 25°.

Suitably, the first (and any subsequent) director blade presents multiple forward acute angles to the linear sweeping path.

In one aspect, the first (and any subsequent) director blade is curved in form.

In another aspect, the first (and any subsequent) director blade is articulated in form.

Suitably, the first (and any subsequent) director blade has a flat tail section.

Suitably, the first director blade is positioned to leave a gap of between 3 and 20mm between the first director blade and the perforated plate. More preferably the first director blade is positioned to leave a gap of between 4 and 8mm between the first director blade and the perforated plate.

Suitably, the director comprises at least one subsequent director blade. In use, the perforated plate and said at least one subsequent director blade are characterized by rotary relative action. Suitably, the at least one subsequent director blade is positioned closer to the perforated plate than the first director blade. Preferably, the at least one subsequent director blade is positioned 0 to 12mm closer to the perforated plate than the first director blade. More preferably the at least one subsequent director blade is positioned 1 to 3 mm closer to the perforated plate than the first director blade. A second subsequent director blade would move along the perforated plate at a lower level to that of a first subsequent director blade.

In one aspect, the transferor comprises a transferor pin.

In another aspect, the transferor comprises a vacuum system. Suitably the vacuum system comprises a vacuum head and a series of vacuum cups.

There is provided a compactor for compacting the powder in the perforation. Suitably, the compactor comprises a compactor pin.

Suitably, the transferor and compactor are integral. More preferably the transferor and compactor are identical.

An additional aspect of the present invention comprises registration means for registering the container (i.e. bringing it into registration) with the perforation.

An additional aspect of the present invention comprises a powder remover for removing excess powder from the perforated plate subsequent to action of the powder director. Suitably, the powder remover comprises a wiper. In use, the wiper and the perforated plate are in rotary relative motion. The wiper is typically a blade composed of stainless steel and moves in close proximity to the surface of the perforated plate to ensure that excess powder is not transferred to the blind cavity.

Suitably, the container is a blind cavity. Preferably, the blind cavity is selected from the group consisting of a blister pocket, an injection moulded plastic pocket, a capsule and a bulk container. A blister pocket or injection moulded plastic pocket may form part of an elongate strip used in medicament delivery devices.

An additional aspect of the present invention comprises a lid applier for applying a lid to the container to protect the contents (e.g. tablet) thereof.

In one aspect, the container comprises a blister pack in laminate form. Suitably, the laminate comprises material selected from the group consisting of metal foil, organic polymeric material and paper. Suitable metal foils include aluminium or tin foil having a thickness of from 5 to 100μm, preferably from 10 to 50μm, such as 20 to 30μm. Suitable organic polymeric materials include polyethylene, polypropylene, polyvinyl chloride and polyethylene terephthalate.

Access to the medicament product comprised within the pockets of the elongate strip form container is by any suitable access means including tearing, piercing or peeling apart the relevant pockets.

One suitable blister pack form medicament container comprises a peelable blister strip. Suitably, the peelable blister strip comprises a base sheet in which blisters are formed to define pockets therein for containing distinct medicament dose portions and a lid sheet which is hermetically sealed to the base sheet except in the region of the blisters in such a manner that the lid sheet and the base sheet can be peeled apart. The base and lid sheets are typically sealed to one another over their whole width except for the forward end portions where they are typically not sealed to one another at all. Thus, separate base and lid sheet forward end portions are presented at the end of the strip. The respective base and lid sheets are peelably separable from each other to (e.g. separately) release the contents of each pocket.

Suitably, the lid sheet comprises at least the following successive layers: (a) paper; adhesively bonded to (b) polyester; adhesively bonded to (c) aluminium foil; that is coated with a heat seal lacquer for bonding to the base sheet. The thickness of each layer may be selected according to the desired properties but is typically of the order of from 5 to 200 micron, particularly from 10 to 50 micron.

Suitably, the base sheet comprises at least the following successive layers: (a) oriented polyamide (OPA); adhesively bonded to (b) aluminium foil; adhesively bonded to (c) a third layer comprising a polymeric material (e.g. polyvinyl chloride).

Various known techniques can be employed to join the lid and base sheet and hence to seal the blisters of the peelable blister strip. Such methods include adhesive bonding, hot metal bonding, hot metal welding, radio frequency welding, laser welding, ultrasonic welding and hot bar sealing. The lid sheet and base sheet of the peelable blister strip are particularly sealable by 'cold form' sealing methods, which are conducted at lower temperatures than conventional heat sealing methods. Such 'cold form' sealing methods are of particular utility where the medicament or medicament formulation for containment within the blister is heat sensitive (e.g.

degrades or denatures on heating). Suitable 'cold form' sealing methods are conducted at a temperature in the range of 150-250°C, more preferably, 210-240°C.

According to a particular aspect there is provided an apparatus for loading each of plural blisters arranged in series on an elongate blister strip with a defined quantity of product, which comprises:

a) a perforated plate having plural perforations therein, said plural perforations being arranged in series;
b) a closure for reversibly closing off each of said plural perforations in the perforated plate;
c) a director for directing powder into each of said closed-off perforations, said director comprising a first director blade spaced from the perforated plate;
d) a compactor for compacting said powder in each of the closed-off perforations to form a tablet; and
e) a transferor for transferring the tablet contents of each of the perforations to a corresponding blister of said elongate blister strip,

wherein the perforated plate and said first director blade are movable in a relative rotary fashion.

Suitably, the apparatus additionally comprises registration means to serially bring each perforation of the perforated plate into registration with a corresponding blister of the blister strip.

Suitably, the apparatus additionally comprises rotational means to rotate the perforated plate and moving means to move the blister strip in linear fashion. At the point of registration, the perforations of the plate are therefore rotating serially and the blisters of the blister strip are moving serially in linear fashion. For good registration, the linear velocities of the perforations and blisters must be matched.

Suitably, the apparatus further comprises powder from which the tablet is to be formed. Preferably, the powder comprises a medicament.

The invention also provides a tablet product obtainable by the method as herein described.

Brief Description of the Drawings

The invention will now be described with reference to the accompanying drawings in which:

Figure 1a, 1b and 1c show the first stage in a method in accord with the present invention;
Figure 2 shows the first stage in an alternative method in accord with the present invention;
Figure 3 shows an optional subsequent compaction stage in the method of Figures 1a, 1b, 1c and 2;
Figure 3A shows a variation of the embodiment of Figure 3;
Figure 4 shows a subsequent transfer stage in the method of Figures 1a, 1b, 1c and 2;
Figure 4A shows a variation of the embodiment of Figure 4;
Figure 5 shows an alternative subsequent stage to the compaction stage of Figure 3 in the filling method of Figures 1a, 1b, 1c and 2;
Figure 6 shows a transfer stage subsequent to the subsequent stage of Figure 5;
Figures 7a and 7b show an alternative transfer stage subsequent to the subsequent stage of Figure 5;
Figure 8a shows rotary apparatus in accord with the present invention; and
Figure 8b shows a schematic (flattened out) side view of the rotary apparatus of Figure 8a.

Detailed Description of the Drawings

Figures 1a, 1b and 1c show the first stages in a tablet production method herein. A rotationally mounted (mounting not visible) perforated plate 10 in contact with a blanking plate 20 creates closed-off perforations 12a, 12b, which (not visible in side view) are in rotary series (i.e. spaced radially from the axis of rotation of the perforated plate 10). On the opposite side of the perforated plate 10 to the blanking

plate 20 is a reservoir of powder 30. The powder 30 comprises a suitable medicament formulation. Situated above the powder reservoir are director blades 40, 42 and wiper blade 50. The director blades may be seen to have following tail sections.

The director blades 40, 42 (i.e. first director blade 40, and subsequent director blade 42) are shown mounted at an angle of approximately 45º to the perforated plate 10. It should however be appreciated that the director blades 40, 42 may be mounted at any angle within a wide range, typically (but not exclusively) at an acute angle and preferably between 1 and 60°, and may be varied according to the properties of the powder to optimise powder direction. When the blades are angled at an acute angle they exert a compressive force on the powder which produces a powder bed with a more uniform density than using perpendicular blades. It should be appreciated that curved or articulated blades may alternatively be used. The tail sections of the director blades 40, 42 are not essential to their action although they may also be angled and exert a further compressive force on the powder. The wiper blade 50 is shown mounted at an angle of approximately 90° to the perforated plate 10, however effective operation of the wiper 50 can be obtained within a wide range of angles.

The powder 30 is directed into the perforations 12a, 12b on rotation of the perforated plate 10 by the action of static director blades 40,42 which thereby move through the powder reservoir 30 on a sweeping rotary path, moving the powder 30 along the rotating perforated plate 10. The first director blade 40 moves through the powder reservoir 30 leaving a thin layer of excess powder 32 still in contact with the perforated plate 10. The second director blade 42 moves relative to the perforated plate 10 at a lower level than the first director blade 40, moving through the thin layer of excess powder 32 and directing powder 30 into any spaces in the perforations 12a, 12b not filled by the action of the first director blade 40. Additional director blades may follow the second director blade 42 if required. Alternatively, the director blades 40, 42 may be passed through the powder reservoir 30 more than once if the powder has poor flow properties. A static wiper 50, typically a blade composed of stainless steel, mounted in rotary series with the two director blades 40, 42 then moves through the powder reservoir 30 in close proximity to the surface of the

rotating perforated plate 10, removing the excess powder 32 from the perforated plate surface 10.

Figure 2 shows the first stage in an alternative method herein. Blanking pins 180a, 180b are inserted into a rotatable perforated plate 110 to create closed-off perforations 112a, 112b. The blanking pins 180a, 180b and closed-off perforations 112a, 112b are each in corresponding rotary series. The volume of the closed-off perforations 112a, 112b may be varied by varying the insertion depth of the blanking pins 180a, 180b. On the opposite side of the perforated plate 110 to the blanking pins 180a, 180b is a reservoir of powder 130. The powder 130 comprises a suitable medicament formulation. The powder 130 is directed into the perforations 112a, 112b (as shown in Figures 1a and 1b) by the action of a director blade 140 which moves across the powder reservoir 130 on a rotary path as the perforated plate 110 is rotated and moves the powder 130 along the perforated plate 110, leaving a thin layer of excess powder 132 still in contact with the perforated plate 110. The director blade shown illustrates a blade with a longer tail section than the blades shown in Figures 1a, 1b and 1c and this tail section is shown angled at about 10° to the rotary path. However it should be appreciated that any blade in accord with the present invention may be used to fill the perforations closed off by the blanking pins. A wiper 150 follows the director blade 140 (as shown in Figure 1c) and moves radially along the powder reservoir 130 in close proximity to the surface of the perforated plate 110, removing the excess powder 132 from the perforated plate surface 110.

Figure 3 shows a subsequent stage to Figures 1a, 1b 1c and Figure 2 in which compaction pins 270a, 270b (mounted in rotary series) are inserted into the closed-off perforations 212a, 212b (also in rotary series) to compact the powder 230 held within the perforation 212a, 212b to form a tablet therefrom. The compaction is generally from 20 to 50% of original powder volume. The figure shows a blanking plate 220 acting to close off the perforations as in Figures 1a, 1b and 1c however it should be appreciated that this stage is also applicable to the situation where blanking pins are used to close off the perforations as in Figure 2. The blanking plate 220 may then be removed from its position in contact with the perforated plate 210 or the blanking pins removed from the closed-off perforations 212a, 212b. The

tablet 235 generally has poor flow properties and therefore remains in the perforations 212a, 212b.

Figure 3A shows a variation of the embodiment of Figure 3 in which the compaction pins 270a, 270b (only two labelled for clarity) have piston drive mechanisms, which enable the pins 270a, 270b to be sequentially lowered in a cascade pattern (e.g. sinusoidal pattern) as the perforations 212a, 212b are rotated past. Dotted line A-B shows a snapshot of the cascade pattern wherein the pins cascade in the direction from A to B, such that at point A the pin is moving down to the plate 210 and at point B it is moving away from the plate 210.

Figure 4 shows a further stage to Figures 1a, 1b, 1c, 2 and 3 in which a blister strip 360 is moved so that it is positioned with blister pockets 362a, 362b into registration with the perforations 312a, 312b, which are in rotary series. It will be appreciated that for a linear blister strip 360 (i.e. having multiple pockets 362a, 362b in linear series) the registration with the perforations 312a, 312b in rotary series may not be exact at all points, but that for a rotary series of sufficient radial characteristic approximate registration is achievable for a certain number (e.g. three or five) of pockets (e.g. see description of Stage C of Figure 8). The solid sections 314a, 314b of the perforated plate 310 mask the surface surrounding the pockets 364. The radially mounted transfer pins 370a, 370b are inserted through the perforated plate 310 and the tablet 335 is transferred to the blister pockets 362a, 362b. The filled blister strip 360 is then lowered and the pins 370a, 370b raised. The blanking plate 320 is relocated against the underside of the perforated plate 310, creating closed-off perforations 312a, 312b, which are each filled with a tablet 335 in the next cycle.

It should be appreciated that the tablet can also be transferred to other types of container, for example an injection moulded container, a capsule or other form of blind cavity.

The blister strip 360 of Figure 4 may be sealed by applying a lid sheet and providing sealing means so that the powder is contained in a medicament container defined by the pocket and elongate strip. Suitable methods of sealing the medicament carrier include the use of adhesives, staples or stamps and welding methods selected from

hot metal welding, radio frequency welding and ultrasonic welding. Such sealing techniques may be used to form a suitable seal around the periphery of the medicament pocket which is capable of being peeled away by the patient or by a suitable trigger release mechanism in a controlled manner when in use.

Figure 4A shows a variation of the embodiment of Figure 4 in which the transfer pins 370a, 370b (only two labelled for clarity) have piston drive mechanisms, which enable the pins 370a, 370b to be sequentially lowered in a cascade pattern (e.g. sinusoidal pattern) as the perforations 312a, 312b are rotated past. Dotted line A-B shows a snapshot of the cascade pattern, wherein as in Figure 3A the pins move in cascade fashion in the direction A to B.

Figure 5 shows an alternative stage subsequent to Figures 1a, 1b, 1c and 2 in which radially mounted compaction pins 470a, 470b are inserted into radially arranged closed-off perforations 412a, 412b to compact the powder held within the perforation 412a, 412b. The force applied to the powder is sufficient to compress the powder 430 enough to form a tablet 435.

Figure 6 shows a transfer stage subsequent to Figure 5 in which the blanking plate 520 (or other blanking method e.g. blanking pins) is removed from its position in contact with the perforated plate 510, allowing the tablets 535 to fall out of the perforations and be collected by a bulk container 566. The radially mounted transfer pins 570a, 570b may be used to help push the tablets 535 through the perforations 512a, 512b. The tablets may then be subjected to further processing steps before packaging. It should be appreciated that the tablets 535 may be transferred to other types of container such as a blister strip following an additional step to register the blister pockets with the perforations 512a, 512b.

It may be appreciated that in variations herein the compaction pins 470a, 470b of Figure 5 and/or the transfer pins 470a, 470b of Figure 6 may be arranged to be sequentially lowered/raised in a cascade type pattern (analogous to that shown in Figures 3A and 4A).

Figures 7a and 7b show an alternative transfer stage subsequent to Figure 5 in which the tablets 635 are transferred by a vacuum head 690 into the container. The radially mounted blanking pins 680a, 680b are raised within the radially arranged perforations 612a, 612b to position the tablets 635 at the top of the perforations 612a, 612b. The vacuum head 690 comprising a series of vacuum cups 692, 694 is moved into position so that each vacuum cup 692, 694 is brought into registration with a perforation 612a, 612b. The vacuum cups 692, 694 then pick up the tablets 635 and the vacuum head 690 is lifted and moved away from the rotating perforated plate 610 and brought into alignment with the blisters 662a, 662b of a blister pack, or into alignment with another suitable container. The tablets 635 are then transferred from the vacuum cups 692, 694 into the blister pack.

It may be appreciated that in variations herein the vacuum head cups 692, 694 of Figures 7A and 7B may be arranged to be sequentially lowered/raised in a cascade type pattern (analogous to that shown in Figures 3A and 4A).

Figure 8a shows in top-view an apparatus suitable for use in the filling method herein. Figure 8b shows the apparatus of Figure 8a in a schematic, flattened out view (i.e. the view along the circumference of the apparatus, as if flattened out). The apparatus comprises a circular stainless steel plate 710 mounted for rotation about axis 711. The plate 710 is provided with three angularly spaced sets (only one labelled for clarity) of dual radial series 712a, 712b of sixty perforations arranged concentrically at a position spaced from the perimeter of the plate 710. A reservoir of powder 730 is provided to the plate 710 and guided by guide blades 732, 750 to adapt a particular configuration on the plate 710 dependent on the stage in the rotational cycle thereof.

The operation of the apparatus involves three distinct stages labelled A, B and C in both of Figures 8a and 8b and illustrated in more detail in the corresponding cutaway drawings of Figure 8a. It will be appreciated that the three stages are sequential (direction of rotation indicated on both Figures) and dependent on the experienced stage in the rotational cycle of the plate 710.

At Stage A, the filling stage, blanking pins 720a are brought upwards to close off the bottom of each perforation 712a of the plate (one closed-off perforation 712a shown in cutaway). Powder 730 is guided towards the closed off perforations 712a, 712b by the action of guide blade 732. Subsequent director blades 740, 742 then direct the powder firmly into the closed off perforations 712a, 712b. It may be seen on Figure 8b that the director blades 740, 742 each present a forward acute angle to the powder bed 730. Excess powder 730 is removed from the surface of the plate 710 adjacent to the filled closed off perforations 712a, 712b by the wiping action of wiping guide blade 750. It may be appreciated that Stage A of Figure 8 corresponds in essential function to the filling step of Figure 2 and that the filling step of Figures 1a, 1b and 1c may be used in alternative embodiments.

At Stage B, the compaction stage, the blanking pins 720a at the bottom of each perforation 712a of the plate (one closed-off perforation 712a shown in cutaway on Figure 8a) remain in place. Compaction pins 770a are now introduced into the top of each closed-off perforation 712a to compact the powder therein to form a tablet 735. The degree (e.g. force) of compaction is selected according to nature (e.g. density) of tablet required. It may be appreciated that Stage B of Figure 8 is analogous to the compaction steps of Figures 3, 3A and 5, which detailed features may be used in alternative embodiments herein.

At Stage C, the transfer stage, the blanking pins 720a are first withdrawn to expose the bottom of each perforation 712a of the plate 710 (one perforation 712a shown in cutaway on Figure 8a). The dual series of sixty blisters 762a, 762b of blister strip 760 are then sequentially brought into registration with the exposed bottom of the corresponding series of filled perforations 712a, 712b. It will be appreciated that this is achieved by moving the blister strip 760 on a linear path as shown. The tablet 735 in the closed off perforations 712a, 712b is then transferred into the blisters 762a, 762b of the blister strip 760 by the action of transfer pin 770a, which is inserted deep into the perforation 712a. It may be appreciated that Stage C of Figure 8 is analogous to the compaction steps of Figures 4, 4A and 6, which detailed features may be used in alternative embodiments herein.

It may also be appreciated that because the linear velocity of the two radial series of perforations 712a, 712b will differ slightly (although they share the same angular velocity) care is needed at Stage C in achieving a suitable registration with the corresponding series of blisters 762a, 762b, which of course, share the same linear velocity. Variations are envisaged in which the perforations 712a, 712b of the two radial series are slightly offset from each other to part compensate for this factor. Other variations are envisaged in which the relative size of the perforations 712a, 712b to the blisters 762a, 762b is selected in order to ensure an acceptable degree of registration (i.e. that which is sufficient to ensure effect transfer of compacted powder).

Post-filling, the blister strip 760 of Figures 8a and 8b is sealed by applying a lid sheet and providing sealing means so that the tablet 735 is contained within the strip 760. Suitable methods of sealing have been described hereinbefore.

The co-ordinated, cascade flowing movement of the blanking pins 720a and compaction pins 770a through the rotary cycle (i.e. through Stages A to C) may be appreciated by reference to Figure 8b.

It may be appreciated that any of the parts of the filling apparatus or container that contact the medicament product may be coated with materials such as fluoropolymer materials (e.g. PTFE or FEP) which reduce the tendency of medicament to adhere thereto. Any movable parts may also have coatings applied thereto which enhance their desired movement characteristics. Frictional coatings may therefore be applied to enhance frictional contact and lubricants (e.g. silicone oil) used to reduce frictional contact as necessary.

The invention is suitable for filling blister packs, or other suitable containers as described hereinbefore, with tabletted medicament products.

Appropriate medicaments may thus be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate (e.g. as the sodium salt), ketotifen or nedocromil (e.g. as the sodium salt); antiinfectives e.g., cephalosporins, penicillins,

streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti- inflammatories, e.g., beclomethasone (e.g. as the dipropionate ester), fluticasone (e.g. as the propionate ester), flunisolide, budesonide, rofleponide, mometasone e.g. as the furoate ester), ciclesonide, triamcinolone (e.g. as the acetonide) or 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol (e.g. as free base or sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g. as hydrobromide), formoterol (e.g. as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g. as acetate), reproterol (e.g. as hydrochloride), rimiterol, terbutaline (e.g. as sulphate), isoetharine, tulobuterol or 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]ethyl-2(3H)-benzothiazolone; adenosine 2a agonists, e.g. 2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (e.g. as maleate); α_4 integrin inhibitors e.g. (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy) acetyl]amino}pentanoyl)amino] propanoic acid (e.g. as free acid or potassium salt), diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium (e.g. as bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon; vaccines, diagnostics, and gene therapies. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament.

In one aspect, preferred components of combinations of active ingredients contain a bronchodilator in combination with an anti-inflammatory. The bronchodilator is suitably a beta-agonist, particularly a long-acting beta-agonist (LABA). Suitable bronchodilators include salbutamol (e.g., as the free base or the sulphate salt), salmeterol (e.g., as the xinafoate salt) and formoterol (eg as the fumarate salt). The anti-inflammatory is suitably an anti-inflammatory steroid. Suitably anti-inflammatory

compounds include a beclomethasone ester (e.g., the dipropionate), a fluticasone ester (e.g., the propionate) or budesonide or any salt or solvate thereof. One preferred combination of components comprises fluticasone propionate and salmeterol, or any salt or solvate thereof (particularly the xinafoate salt). A further combination of components of particular interest is budesonide and formoterol or any salt or solvate thereof (e.g. formoterol as the fumarate salt).

Suitable tablets herein may comprise pure drug, but more appropriately, the medicament active(s) are formulated together with other pharmaceutically acceptable ingredients. Suitable further ingredients include organic carriers such as polysaccharides (i.e. starch, cellulose and the like), lactose, glucose, mannitol, amino acids, and maltodextrins, and inorganic carriers such as calcium carbonate or sodium chloride. Binders may be employed to assist with tablet binding.

Particles of powdered medicament for use in the tabletting process may be produced by conventional techniques, for example by micronisation, milling or sieving. Particles may comprise active agents, surfactants, wall forming materials, or other components considered desirable by those of ordinary skill.

Carriers and other ingredients may be included with the medicament via well-known methods, such as by admixing and co-precipitating. Blends of excipients and drugs are typically formulated to allow the precise metering and dispersion of the blend into tabletted doses.

It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto.

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described therein. They may take the form of product, method or use claims or may include, by way of example and without limitation, one or more of the following claims: